PATENT
Atty. Docket No.: 018512-000120US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Lawrence SALKOFF et al.

Application No.: 09/176,664

Filed: October 21, 1998

For: PH SENSITIVE POTASSIUM CHANNEL IN SPERMATOCYTES

Examiner: Nirmal S. Basi

Art Unit: 1646

APPELLANT'S BRIEF UNDER 37 C.F.R. 1.192

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P.O. Box 1450
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Sir:

This brief is filed in triplicate pursuant to 37 C.F.R. §1.192(a), following the Notice of Appeal, mailed June 30, 2003. Also submitted in triplicate with this brief is authorization to pay the fee as set forth in 37 C.F.R. §1.17(c).

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I. REAL PARTY IN INTEREST

The real parties in interest in U.S. Application No. 09/176,664 are The Washington University and ICAgen, Inc.

II. RELATED APPEALS

No other appeals or interferences known to Appellant, Appellant's legal representative, or assignees will directly affect, or be directly affected by, or have bearing on, a decision by the Board of Patent Appeals and Interferences in this pending appeal.

III. STATUS OF THE CLAIMS

Claims 1-44 were originally filed. Claims 44-48 were later added. Claims 2, 3, 6, 7, 10-25, 28-44, and 48 have been canceled. Claims 20, 21, and 24-39 are withdrawn from consideration. Claims 1, 4, 5, 8, 9, 26, 27, and 45-47 are pending in the present application. In the Final Office Action mailed January 29, 2003, the Examiner has rejected claims 1, 4, 5, 8, 9, 26, 27, and 45-47 under 35 U.S.C. §101, alleging lack of a specific and substantial credible utility. The Examiner has also rejected the claims under 35 U.S.C. §112, first paragraph, alleging failure to enable the claimed invention based on utility as well as claim scope.

IV. SUMMARY OF THE INVENTION

The invention relates to the first isolation and characterization of Slo3, a pH sensitive potassium channel, which is primarily expressed in spermatocytes. The instant application provides both the nucleotide and amino acid sequences of human and mouse Slo3, as well as methods of assaying for modulators of Slo3, antibodies to Slo3, and methods of detecting Slo3 nucleic acids and polypeptides.

The pending claims are directed to an isolated nucleic acid encoding a polypeptide monomer of a pH sensitive potassium channel. This monomer has the following attributes: (i) it is capable of forming a potassium channel that has a unit

conductance of approximately 80-120 pS and has increased potassium channel current activity above approximately intracellular pH of 7.1, when the monomer is expressed in a *Xenopus* oocyte; and (ii) it is encoded by a nucleic acid that selectively hybridizes under highly stringent hybridization conditions to a nucleic acid comprising a nucleotide sequence of SEQ ID NO:2, SEQ ID NO:17, or SEQ ID NO:19, wherein the hybridization reaction is incubated at 42°C in a solution comprising 50% formamide, 5x SSC, and 1% SDS and washed at 65°C in a solution comprising 0.2x SSC and 0.1% SDS.

V. ISSUES ON APPEAL

1. The rejection for lack of utility is improper because the present invention meets the statutory requirement and because the Examiner has not provided any objective reasons why the asserted utilities are not credible.

2. The rejection for lack of enablement is improper because the present invention does not lack utility.

3. The rejection for lack of enablement is further improper because the specification adequately enables the claimed invention under the prevailing case law.

VI. CLAIM GROUPING

Claims 1, 4, 5, 8, 9, 26, 27, and 45-47 do not stand and fall together. Claims 4, 5, 8, and 9, which are directed to an isolated nucleic acid that either encodes an reference amino acid sequence (SEQ ID NO:1, 16, or 18) or has a reference nucleotide sequence (SEQ ID NO:2, 17, or 19), can stand alone as properly enabled even if claims 1, 26, 27, and 45-47 are held not adequately enabled.

VII. ARGUMENT

A. The Rejection for Lack of Utility Is Improper

Claims 1, 4, 5, 8, 9, 26, 27, and 45-47 stand rejected under 35 U.S.C. §101 because the Examiner alleges that the claimed invention lacks either a well-established utility or a credible specific and substantial asserted utility.

Appellant respectfully traverses this rejection and argues that the rejection is improper. The present invention resides in the identification of Slo3 nucleic acids. Utility under 35 U.S.C. §101 is present because the identification of Slo3 nucleic acids permits one of skill in the art to screen for agonists or antagonists of the Slo3 channels, which can be used, *e.g.*, for treating fertility disorders related to sperm physiology or as contraceptives.

1. Standard to Assess Utility

According to MPEP §2107, the Examiner should review the claims and the supporting written description to determine whether the utility requirement under 35 U.S.C. §101 is met. No rejection based on lack of utility should be made if an invention has a well-established utility, *i.e.*, a utility that will be immediately appreciated by one of ordinary skill in the art based on the characteristics of the invention, regardless any such utility has been asserted. Neither should any rejection be made for lack of utility if an applicant has asserted a specific and substantial utility that would be considered credible by one of ordinary skill in the art.

In most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101. MPEP §2107.02 III A. The Court of Customs and Patent Appeals stated in *In re Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of §101 for the entire claimed subject matter unless there is

> a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

In re Langer, 183 USPQ 288, 297 (CCPA, 1974, emphasis in original). To overcome the presumption of sufficient utility as asserted by an applicant, the Examiner must carry the initial burden to make a *prima facie* showing of lack of utility and provide a sufficient evidentiary basis for the conclusion. In other words, the Examiner "must do more than merely question operability--[he] must set forth factual reasons which would lead one skilled in the art to question objective truth of the statement of operability." *In re Gaubert*, 187 USPQ 664, 666 (CCPA 1975).

MPEP §2107.02 IV further states, a detailed explanation should be given for a utility rejection as to why the claimed invention has no specific and substantial asserted utility. Documentary evidence should be provided when possible. Otherwise the Examiner should specifically explain the scientific basis for his factual conclusions.

2. The Asserted Utility and the Examiner's Rejection

The instant application asserts a specific and substantial utility of the claimed invention. For example, it is asserted on page 12, lines 21-34, of the specification that the identification of Slo3 nucleic acids and polypeptides allows screening for modulators of Slo3 channels using *in vitro* or *in vivo* assays. These modulators are useful for treating infertility or as contraceptives. The specification further states that Slo3 expression can be used as a diagnostic marker for spermatocytes.

Appellant has in addition submitted a declaration pursuant to 37 C.F.R. §1.132 by Dr. Timothy Jegla, formerly the Chief Scientist and Head of Molecular Sciences at ICAgen, Inc. (submitted January 9, 2002), to establish the physiological function of the Slo3 channel and the therapeutic use of its modulators.

In the Office Action mailed September 13, 2001, the Examiner alleges that the instant specification fails to establish a specific and substantial asserted utility of the claimed invention. While conceding that the claimed nucleic acid of instant application

encodes a potassium channel, the Examiner contends that the specification does not disclose the specific function of the Slo3 channel or any disease states related to the dysfunction of this potassium channel, and that the asserted utility is a hypothesis or conjecture based on the general functions of potassium channels and sequence homology (see page 3 line 19 to page 5 line 2 of the Action mailed September 13, 2001). The Examiner offers no documentary evidence or scientific basis for the conclusion.

In the Office Action mailed May 7, 2002, the rejection for lack of utility is maintained. The Examiner simply reiterates that the specification has not provided evidence to support the asserted biological functions of the Slo3 channels and the use of their modulators (see page 6 line 3 to page 7 line 6 of the Action mailed May 7, 2002).

In the Final Office Action mailed January 29, 2003, the utility rejection is sustained from the previous Actions. The Examiner questions Appellant's assertion of Slo3 channel's physiological function and association with fertility conditions, yet again does not give any evidence or objective reason why the asserted utility is not credible. In fact, the Examiner concedes that "[p]ersons of skill in the art may expect that the Slo3 channel may play a role in the spermatocytes," but insists that "its role is not known at present" and that there is no showing [Slo3 modulators] would modulate sperm function and ..... may be used to treat infertility conditions due to Slo3's involvement in capacitation and acrosome reaction" (see page 4, lines 4-10, of the Final Office Action).

3. The Claimed Slo3 Polynucleotides Are Useful for Screening of Compounds for Treating Fertility Disorders

As described in the present application, the present inventors cloned, for the first time, the mouse and human polynucleotide sequence encoding Slo3, a pH sensitive potassium channel. The inventors also identified the amino acid sequence of Slo3 and determined the tissue-specific expression pattern of Slo3 at the mRNA level. Furthermore, the inventors recombinantly expressed Slo3 and fully characterized the electrophysiological properties of the Slo3 channel.

Slo3 Expression in Spermatocytes

The Slo3 channel is a pH sensitive potassium channel specifically and primarily expressed in the spermatocytes. The Examiner expresses doubts about this assertion, stating, "[t]he potassium channel of instant invention was isolated from testis. The specification does not disclose that the claimed invention was isolated from spermatocytes" (page 3 lines 3-5 of the Final Office Action).

Appellant respectfully note that although Slo3 coding sequence was isolated from testis, the instant specification does show that Slo3 is abundantly expressed in spermatocytes. In Example II (page 56 line 30 to page 59 line 13), mouse testes were dissected, frozen, and sectioned for *in situ* hybridization using a labeled mSlo3 nucleotide sequence. In describing the results of the hybridization assays, the specification states:

> ***Labeling was observed in annular rings corresponding to the positions of spermatocytes in seminiferous tubules.*** Positive hybridization signals appeared as white dots on darkfield micrographs. ***Dense circular patterns of hybridization signals corresponded to the annular clusters of spermatocytes.*** The annular structure show the cross-section of a single seminiferous tubule, composed largely of developing spermatocytes. Stem cells and primary spermatocytes were at the outer edges, while more mature spermatocytes were found near the lumen. Supporting Sertoi cells and Leydig cells, difficult to distinguish at this resolution, were present in lower numbers. ***Hybridization signal at the inner margins of the circular patterns of seminiferous tubules corresponded to the positions of secondary spermatocytes and possibly even spermatids.*** Dark-field microscopy of the same view shows ***intense hybridization of antisense probe with mSlo3 mRNA in developing spermatocytes.*** The outer edges and interstices between tubules are unstained, suggesting that primary and secondary spermatocytes are the predominant cell type expressing the message, rather than spermatogonia (spermatic stem cells). Staining of the innermost regions of the tubule suggests that even early spermatids may be expressing the message. ***The high density of labeling demonstrates a high degree of mSlo3 expression in spermatocytes.***

(page 58 line 23 to page 59 line 5 of the specification, emphasis added). Appellant thus submit that the specification has established the expression of Slo3 in spermatocytes.

Therapeutic Use of Slo3 Modulators

It is well known in the art that intracellular pH and membrane potential have a profound effect on the viability of mammalian sperm. For example, alkaline pH is necessary for sperm capacitation and the acrosome reation (*see* Arnoult *et al.*, *J. Cell. Biol.* **134**:637-645 (1996) and Zeng *et al.*, *Dev. Biol.*, **173**:510-520 (1996), submitted as Exhibits A and B with Appellant's communication to the PTO filed on January 9, 2002). Figures 3 and 4 of the instant specification show the expression of mouse Slo3 in *Xenopus* oocytes using standard methodology and demonstrate that the claimed nucleic acid encodes a pH-responsive channel. Dr. Jegla further indicates in his declaration that based on the disclosure of the present specification (including Figures 3 and 4), a skilled artisan would believe that a Slo3 channel plays an important role in sperm capacitation by modulating potassium permeability (paragraph 8 of Dr. Jegla's declaration).

Because one of skill in the art would expect the Slo3 channel to play a physiological role in sperm capacitation, an obligatory step in fertilization, it would therefore be apparent to an artisan that Slo3 can be an excellent therapeutic target for modulating sperm function using Slo3 openers or blockers. Compounds capable of modulating Slo3 activity can be used for treating infertility caused by reduced sperm function or used as a type of contraceptive (paragraph 9 of Dr. Jegla's declaration).

The present application provides nucleotide sequences of Slo3 channels, methods of assaying Slo3 channels function, and methods of assaying for compounds increase or decrease ion flux of Slo3 channels. A skilled artisan, after reading the present application, would therefore be able to routinely identify modulators of Slo3 channels and determine if a candidate compound can affect the physiology of sperm by altering Slo3 channel activity.

The Examiner argues in the Final Office Action that calcium channel activity is responsible for achieving the alkaline pH necessary for sperm capacitation and that there is no evidence supporting Slo3's involvement in this process (page 4 lines 2-6 of the Final Office Action). Besides the issue of the initial burden, which is discussed above, Appellant further notes that even if Slo3 is not directly involved in the initiation of sperm capacitation, alteration of Slo3 activity can still have an effect on the intracellular pH via changed potassium passage through the Slo3 channel. Therefore, the Slo3 channel can nonetheless be targeted for modulating sperm function and Slo3 modulators can nonetheless be used as therapeutic agents for fertility disorders or as contraceptives.

Appellant thus contends that the asserted utility for the present invention is one supported by the general knowledge in the relevant field and a person of ordinary skill in the art would find such utility credible.

4. The Asserted Utility is Specific, Substantial, and Credible

Appellant maintains that the disclosure of Slo3 coding sequences for pH-activated potassium channels expressed in spermatocytes and the electrophysiological characterization of the Slo3 channels, combined with the methods disclosed in the specification and the level of skill in the art, is sufficient to establish a credible specific and substantial utility under the definitions provided by the MPEP.

Specific Utility

Appellant asserts that the present invention has a specific utility. Specific utility is defined by the MPEP as a utility that is specific to the subject matter claimed. The MPEP explains that applications show sufficient specific utility when applicants disclose a "specific biological activity" and reasonably correlate that activity to a "disease condition." MPEP §§2107.01 and 2107.02. In the present application, Appellant identifies the nucleic acid and amino acid sequences of Slo3, demonstrates the expression pattern of Slo3, teaches the recombinant expression of Slo3, and illustrates the

electrophysiological characteristics of the Slo3 channels. Appellant further discloses a "disease condition" (*i.e.*, fertility disorder) that correlates with a "biological activity" (*i.e.*, the opening and closing of a Slo3 channel). This application demonstrates that Slo3 channels mediate potassium ion flux in spermatocytes in response to changes in intracellular pH and membrane potential. The application further provides methods for identifying compounds capable of modulating Slo3 channel activity. These compounds can therefore be used, *e.g.*, for treating fertility disorders related to sperm function, or as a type of contraceptive. Appellant thus submits that the present invention has a specific utility, namely that Slo3 channels can mediate potassium flux in spermatocytes, which is clearly specific for the claimed Slo3 channels and not any ion channels.

Substantial Utility

Appellant also asserts that the present invention has a substantial or "real-world" use. This invention provides Slo3 channel polynucleotide and polypeptide sequences. The application also demonstrates that Slo3 channels modulate potassium flux in spermatocytes and teaches how to identify agonists and antagonists of the Slo3 channels. For example, on pages 44-46 of the specification, Appellant provides assays that can be used to test for inhibitors and activators of Slo3 channels, *e.g.*, assays that involve measuring current, measuring membrane potential, measuring ion flux, or measuring patch-clamp electrophysiology. The present invention therefore has a real-world use in the modulation of spermatocyte physiology, as well as in the identification of compounds that modulate Slo3 channels and thus can be useful as therapeutic agents for treating diseases or conditions related to sperm function, such as infertility.

Credible Utility

Finally, Appellant contends that the asserted utility of the present invention is credible, *i.e.*, would be believable to one of skill in the art. Appellant submits that an ordinarily skilled artisan, after reading this application, would know (a) how to identify Slo3 channels (b) how to identify agonists or antagonists of Slo3 channels

(c) how to use these agonists or antagonists so identified to modulate potassium flux in spermatocytes. Because of the crucial role intracellular pH and membrane potential play in sperm capacitation, one skilled in the art would believe that the identification of a new potassium channel sensitive to pH and membrane potential changes is useful for developing new therapeutics for treating disorders caused by abnormal sperm function (see paragraph 9 of Dr. Jegla's declaration).

5. The Examiner's Rejection Is Based on a Conclusory Statement without Objective Reasons

Despite the assertion of a specific and substantial utility of the claimed invention in the specification and Dr. Jegla's declaration supporting the asserted utility, the Examiner maintains the utility rejection based on personal disbelief of the asserted utility rather than credible scientific evidence. For example, the Examiner states in the September 3, 2001, Office Action that "the hypothesized function [of Slo3 channels] is based entirely on conjecture from homologous polypeptides" (page 4 lines 16-17 of the Action). The Examiner further states that the specification does not show that "the claimed nucleic acids.....useful to identify drugs that affect [Slo3 channels] and modulate their activity" or that "disorders can be affected by interfering with the activity [of Sol3 channels] using [the] claimed polynucleotides" (page 5 lines 1- 2 of the Action). Similarly the Examiner states in the Final Office Action, "there is no disclosure to show [that Slo3] is directly the cause of or even involved in initiating sperm capacitation, e.g., by increasing potassium permeability" (page 4 lines 5-6 of the Final Office Action). The Examiner goes on to say that "there is no showing [that Slo3-modulating] compounds would modulate sperm function and that said compounds may be used to treat infertility conditions due to Slo3's involvement in [sperm] capacitation and acrosome reaction" (page 4 lines 8-10 of the Final Office Action). Besides voicing doubts, the Examiner provides no documentary evidence or scientific explanation as to why the asserted utility is not credible.

Raising a rejection for lack of utility in such a manner is inconsistent with the proper practice described in the MPEP, which places the initial burden on the Examiner, not Appellant, to provide evidence to support a factual conclusion of the credibility of an asserted utility. In fact, MPEP §2107.02 III.B. specifically cautions Office personnel that, once an assertion of a particular utility is made, "that assertion cannot simply be dismissed ..... as 'wrong,' even when there may be reason to believe the assertion is not entirely accurate." Instead, the Examiner must provide an explanation setting forth the reasoning used in concluding that the asserted specific and substantial utility is not credible; support for factual findings relied upon in reaching the conclusion; and an evaluation of all relevant evidence of record, including utilities taught in the closest prior art. MPEP §2107.02 IV.

The Examiner has provided none of the above. The pending claims are rejected for lack of utility simply because the Examiner does not believe the specific and substantial utility asserted by Appellant. Appellant respectfully submits that the Examiner's disbelief, without more, cannot properly sustain the rejection.

6. Finding Sufficient Utility in the Present Application is Consistent with the Policy of Encouraging Early Disclosure

Our patent law places much emphasis on encouraging early disclosure of inventions. This is a particularly relevant policy consideration in case law involving the utility standard under 35 U.S.C. §101. In *Brenner v. Manson*, 148 USPQ 689 (US Sup. Ct. 1966), for instance, the Supreme Court ruled that a process to produce a compound may be patented only if the compound has "substantial utility," "specific benefit ... in currently available form." Whether granting patent protection to the discovery of a new process or compound with a yet unknown practical utility would encourage prompt disclosure of inventions was one factor the Court carefully considered and to a significant extent relied upon in reaching the landmark decision. 148 USPQ at 695.

In *Nelson v. Bowler*, 206 USPQ 881 (CCPA 1980), the CCPA was confronted with a situation where the claimed compound, 16-phenoxy-substituted prostaglandin (PG), was shown to have some pharmacological activity, *i.e.*, causing changes in blood pressure in the rat blood pressure (BP) test and stimulation of smooth muscles in the gerbil colon smooth muscle stimulation (GC-SMS) test, yet no specific therapeutic use for the compound was established. In deciding the question of utility, the CCPA stated:

> Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illness and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many as compounds as possible, we conclude that adequate proof of any such activity constitute a showing of practical utility.

Nelson, 206 USPQ at 883. The present case is analogous to *Nelson*. Because abnormal ion influx and altered intracellular pH can interfere with sperm capacitation and acrosome reaction, compounds capable of modulating ion channels, such as the Slo3 channels, are useful as therapeutic agents for treating these conditions. Assays for screening of ion channel modulators is thus beneficial to the public and the disclosure of how to perform these assays should be encouraged. The present application provides just this kind of disclosure. To hold that the present invention lacks sufficient utility under 35 U.S.C. §101 to warrant patent protection would be inconsistent with the underlying policy of case law and create a strong disincentive for researchers to disclose their inventions of this type.

7. Summary

In light of the foregoing discussion, Appellant believes that the utility rejection under 35 U.S.C. §101 is improper and should be withdrawn.

B. The Rejection for Inadequate Enablement Based on Utility Is Improper

The Examiner has also rejected claims 1, 4, 5, 8, 9, 26, 27, and 45-47 as not being enabled, alleging that the claimed invention is not supported by either a credible specific and substantial asserted utility or a well-established utility. As discussed above, the claimed invention has a credible specific and substantial utility. Appellant therefore believes that the enablement rejection under 35 U.S.C. §112, first paragraph, is improper and should be withdrawn.

C. The Rejection for Inadequate Enablement Based on Claim Scope Is Improper

The Examiner has further rejected claims 1, 4, 5, 8, 9, 26, 27, and 45-47 under 35 U.S.C. §112, first paragraph, alleging that the invention is not adequately enabled for the scope of the pending claims. Specifically, the Examiner contends that the recitation of hybridization conditions allows the claims to encompass polynucleotide sequences encoding polypeptides that are functionally dissimilar to the Slo3 channels and have no known use.

As will be discussed in detail below, the claimed invention as described in the present application fully complies with the enablement requirement as set forth by the MPEP and prevailing case law. Appellant thus submits that the enablement rejection is improper and should be withdrawn.

1. Standard for Enablement

According to the MPEP, to satisfy the enablement requirement, the information contained in a patent specification must be sufficient to inform one skilled in the relevant art how to both make and use the claimed invention. MPEP §2164. Whether the enablement requirement is met depends on whether undue experimentation is necessary for one of skill in the art to practice the invention in light of the disclosure. MPEP §2164.01.

As set forth by the Federal Circuit in *in re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), multiple factors should be considered when determining whether any necessary experimentation is undue. These factors include:

(a) the breadth of the claims;

(b) the nature of the invention;

(c) the state of the prior art;

(d) the level of one of ordinary skill;

(e) the level of predictability in the art;

(f) the amount of direction provided by the inventor;

(g) the existence of working examples; and

(h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Furthermore, to reject a claim for lack of enablement, the Examiner must carry the initial burden to establish a reasonable basis for questioning the enablement provided by the specification. MPEP §2164.04.

2. No Undue Experimentation Is Necessary to Practice the Claimed Invention

(a) The Breadth of the Claims

The pending claims are drawn to nucleic acids encoding pH sensitive potassium channels. It is Appellant's intent to include in the claim scope nucleic acids encoding allelic variants and man-made muteins that retain the polypeptide's normal function. For example, the specification states that polymorphic variants of Slo3 are part of the invention and provides three substitution variants of mouse Slo3 and three substitution variants of human Slo3, *e.g.*, valine substituted by isoleucine at position 23, isoleucine substituted by leucine at position 6, etc. (page 12 lines 11-20 of the specification).

The claimed nucleic acids are defined by shared functional features (*i.e.*, encoding a polypeptide monomer capable of forming a potassium channel having a unit

conductance of approximately 80-120 pS and having increased potassium channel current activity above approximately intracellular pH of 7.1 when expressed in a *Xenopus* oocyte) and structural features (*i.e.*, capable of hybridizing under highly stringent conditions to a polynucleotide comprising SEQ ID NO:2, 17, or 19). Because a person of ordinary skill in fields of electrophysiology and molecular biology can easily determine the terms used to define the functional and structural features, the claim scope is set forth clearly and the claims are thus not overly broad or vague.

(b) The Nature of the Invention

The present invention resides in the discovery of a novel pH sensitive potassium channel, Slo3. As stated above, the claimed polynucleotides are defined by their shared functional and structural characteristics, which can be routinely tested and determined by employing standard techniques in the relevant research field.

(c) The State of the Prior Art

The present invention relates to the discovery of a novel potassium channel, Slo3. Prior to the present invention, there already existed a significant amount of knowledge related to ion channels, including potassium channels. In particular, some members of the Slo channel family had been identified and characterized. For instance, *Drosophila* Slo1 gene had been cloned and shown to encode a calcium-activated potassium channel present in both neurons and muscles; whereas the mammalian homologue, *e.g.*, mouse and human Slo1, had also been identified and characterized (see page 1 line 29 to page 2 line 21 of the specification).

The physiology of spermatocytes, particularly the cellular events associated with sperm capacitaion and acrosome reaction, had also been well studied and documented in the prior art. For instance, it was known at the time the present invention was made that changes in membrane potential, intracellular pH, or cytoplasmic Ca^{2+} concentration can have profound influences on sperm function (page 2 line 22 to page 3 line 10 of the specification).

(d) The Level of One of Ordinary Skill in the Art

The relevant field of the present invention is electrophysiology and molecular biology. In this research field, the substantive knowledge was abundant (which is discussed above) and the techniques for conducting these types of studies were well established and highly sophisticated. In short, the ordinary level of technical skill in the relevant art was high.

(e) The Level of Predictability in the Art

The predictability in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. What is known in the art provides evidence as to the question of predictability. MPEP §2164.03. In the present case, the basic techniques in the art of molecular biology, such as techniques for cloning/subcloning, transfection, recombinant expression, and nucleic acid hybridization, have been in existence for over two decades and have since improved dramatically to reach a high level of technical sophistication and predictability. As an example, the book *Molecular Cloning* had presented its third edition in 2001. In addition, as discussed above, much is known about the electrophysiological features of the other members of the Slo ion channel family and the physiology of sperm, particularly sperm capacitation and acrosome reaction, which have been the focus of extensive studies. Therefore, a significant level of predictability exists in the relevant art.

(f) The Amount of Direction Provided by the Inventor

The present application provides ample direction for an artisan to practice the claimed invention. For example, the application provides cloning methods for isolating the polynucleotide sequences encoding Slo3 (page 29 line 26 to page 32 line 9; Example I on page 55 line 7 to page 56 line 28; Example V on page 61 line 32 to page 63 line 2); the application also teaches the methods for expressing Slo3 in prokaryotic and eukaryotic cells (page 32 line 12 to page 34 line 21; Examples II and III on page 56 line 31 to page 60 line 2) and purifying recombinant Slo3 (page 34 line 24 to page 37 line 22);

the application further describes the methods for immunological detection of Slo3 (page 37 line 25 to page 44 line 8); the application in addition offers assays for analyzing Slo3's electrophysiological characteristics (Example IV on page 60 line 5 to page 61 line 29) and assays for screening compounds that modulate Slo3 ion flux (page 44 line 11 to page 48 line 20). As such, a large amount of detailed direction is given in the present disclosure for practicing the claimed invention.

(g) The Existence of Working Examples

The present application provides three working examples: SEQ ID NOs:2, 17 an 19, which weigh in favor of the finding of an enabling disclosure.

(h) The Quantity of Experimentation Needed to Make or Use the Invention

Appellant does not dispute that some experimentation may be necessary to practice the present invention as defined by the pending claims. Yet "the test [of undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 190 USPQ 214, 217-19, (CCPA 1976)).

In the instant case, any necessary experimentation for practicing the claimed invention would be routine for an ordinarily skilled artisan who is familiar with the well established techniques of electrophysiology and molecular biology. These techniques, as discussed above, have been constantly employed and improved by the skilled artisans in the relevant field of research over the last twenty years or so. Today these techniques are highly reliable and merely routine to an artisan of ordinary skill. On the other hand, the specification does provide "a reasonable amount of guidance with respect to the direction in which the experimentation should proceed," as discussed in an earlier section.

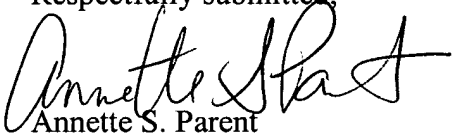
3. Summary

Appellant does not believe that the above factors, when considered as a whole, support the finding of necessary undue experimentation. Accordingly, Appellant respectfully submits that the enablement rejection under 35 U.S.C. §112 is improper and should be withdrawn.

VIII. CONCLUSION

In view of the foregoing, Appellant believes all claims now pending in this Application are in condition for allowance.

Respectfully submitted,



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APPENDIX: PENDING CLAIMS

1. (Previously presented) An isolated nucleic acid encoding a polypeptide monomer of a pH sensitive potassium channel, the monomer:

(i) forming a potassium channel having a unit conductance of approximately 80-120 pS and having increased potassium channel current activity above approximately intracellular pH of 7.1, when the monomer is expressed in a *Xenopus* oocyte; and

(ii) encoded by a nucleic acid that selectively hybridizes under highly stringent hybridization conditions to a nucleic acid comprising a nucleotide sequence of SEQ ID NO:2, SEQ ID NO:17, or SEQ ID NO:19, wherein the hybridization reaction is incubated at 42°C in a solution comprising 50% formamide, 5x SSC, and 1% SDS and washed at 65°C in a solution comprising 0.2x SSC and 0.1% SDS.

4. (As filed) An isolated nucleic acid of claim 1, wherein the nucleic acid encodes SEQ ID NO:1.

5. (As filed) An isolated nucleic acid of claim 1, wherein the nucleic acid encodes SEQ ID NO:16 or 18.

8. (As filed) An isolated nucleic acid sequence of claim 1, wherein the nucleic acid has a nucleotide sequence of SEQ ID NO:2.

9. (Previously presented) An isolated nucleic acid sequence of claim 1, wherein the nucleic acid has a nucleotide sequence of SEQ ID NO:17, or SEQ ID NO:19.

26. (Previously presented) An expression vector comprising a nucleic acid of claim 1.

27. (As filed) A host cell transfected with the vector of claim 26.

45. (Previously presented) The nucleic acid of claim 1, wherein the nucleic acid encodes a polypeptide monomer having a calculated molecular weight of between 120-156 kDa, the molecular weight calculated from amino acid sequence.

46. (As filed) The nucleic acid of claim 1, wherein the nucleic acid encodes a polypeptide monomer forming a homomeric potassium channel.

47. (As filed) The nucleic acid of claim 1, wherein the nucleic acid encodes a polypeptide monomer forming a heteromeric potassium channel.